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From: Gambel, Phillip
Sent: Wednesday, June 26, 2002 8:16 AM
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7/7/42 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09066077 96416165 PMID: 8819071

The role of the CD40 antigen on malignant B cells.
Planken E V; Willemze R; Kluin-Nelemans J C
Department of Hematology, Leiden University Hospital, The Netherlands.
Leukemia & lymphoma (SWITZERLAND) Jul 1996, 22 (3-4) p229-35, ISSN
1042-8194 Journal Code: 9007422

Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
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An increasing amount of literature has been published concerning the interaction of the CD40 antigen and its ligand with regard to normal B cell ontogeny. In this review, an overview of the CD40 antigen and the CD40 ligand is given, focussing on their possible role in B cell malignancies. Data on the expression of the CD40 antigen on various B cell malignancies (acute and chronic leukemias, non-Hodgkin's lymphoma and multiple myeloma) are presented. The recently developed novel culture "CD40 system" is described. This system is a powerful tool used to culture normal B cells, but also most malignant B cells. We demonstrate in addition a more prominent role of the human Fc receptor presenting murine fibroblasts in the "CD40 system", especially in relation to cultured plasma cells. Finally, some important applications of the "CD40 system" are also summarized. (63 Refs.)

Record Date Created: 19970116

7/7/34 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09412291 BIOSIS NO.: 199497420661

Phenotypic and functional characterization of T-BAM (CD40
ligand)+ T-cell non-Hodgkin's lymphoma.

AUTHOR: Inghirami Giorgio(a); Lederman Seth; Yellin Michael J; Chadburn Amy
; Chess Leonard; Knowles Daniel M

AUTHOR ADDRESS: (a)New York Univ., Dep. Pathology, 560 First Ave., New
York, NY 10016**USA

JOURNAL: Blood 84 (3):p866-872 1994

ISSN: 0006-4971

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

7/7/31 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09860255 BIOSIS NO.: 199598315173

Functional Expression of Adhesion Receptors and Costimulatory Molecules by
Fresh and Immortalized B-Cell Non-Hodgkin's Lymphoma Cells:

AUTHOR: Vyth-Dreese Florry A(a); Dellelijn Trees A M; Van Oostveen Johan W;
Feltkamp Constance A; Hekman Annemarie

AUTHOR ADDRESS: (a)Div. Immunol., Netherlands Cancer Inst., Plesmanlaan
121, 1066 CX Amsterdam**Netherlands

JOURNAL: Blood 85 (10):p2802-2812 1995

ISSN: 0006-4971

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Peripheral blood lymphocytes of a patient with follicular B-cell non-Hodgkin's lymphoma (B-NHL) were immortalized in vitro by Epstein-Barr virus (EBV). Eight cell lines were obtained (termed BNS1, BNS2-1 through BNS2-7), which showed a pattern of idiotypic (id) Ig surface expression and Ig JH and kappa gene rearrangement, identical to that of the parent cells (termed NS), confirming their neoplastic origin. Induction of allogeneic T-cell proliferation by NS cells was mediated by HLA-DR, leukocyte function-associated antigen-I (LFA-1), LFA-3, B7-1/CD80, and CTLA4 and resulted in the upregulation (LFA-3, intercellular adhesion molecule-1 (ICAM-1), CD40) and induction (B7-1/CD80, B7-2/CD86, L16/activated LFA-1) of accessory molecules on NS cells. In turn, responder T lymphocytes were induced to express B7-1/CD80, B7-2/CD86, CD40 ligand (CD40L), ICAM-1, L16/activated LFA-1, and HLA-DR, reflecting bidirectional signaling between T lymphocytes and B-NHL cells. Preactivation of NS cells by EBV transformation or CD40 engagement resulted in enhanced expression of accessory molecules and abolished the requirement for accessory cells during allostimulation. These resting and activated clonal B cells will be useful in further dissecting the requirements for B-NHL costimulation.

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10064605 BIOSIS NO.: 199598519523

CD40 ligand is constitutively expressed in a subset of T cell lymphomas and on the microenvironmental reactive T cells of follicular lymphomas and Hodgkin's disease.

AUTHOR: Carbone Antonino(a); Gloghini Annunziata; Gruss Hans-Jurgen; Pinto Antonio

AUTHOR ADDRESS: (a)Div. Pathol., Centro Regionale Riferimento Oncol., IRCCS, via Pedemontana Occidentale, Aviano I-**Italy

JOURNAL: American Journal of Pathology 147 (4):p912-922 1995

ISSN: 0002-9440

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Although CD40 has been extensively studied in Band T-cell non-Hodgkin's lymphomas (NHLs)/leukemias, and more recently in Hodgkin's disease (HD), little is known about the expression of its ligand (CD40L) in lymphoproliferative disorders other than T-cell NHLs/leukemias. A series of 121 lymphoma/leukemia samples, including 35 cases of HD, 34 T-cell and 39 B-cell NHLs, 2 cases of adult T-cell leukemia/lymphoma, and 11 cases of T-cell acute lymphoblastic leukemia, were evaluated for CD40L expression by immunostaining of frozen tissue sections and flow cytometry with the anti-CD40L monoclonal antibody M90. CD40L was constitutively expressed by neoplastic cells in 15 of 36 (42%) T-cell NHLs/adult T-cell leukemia/lymphomas, almost invariably those displaying the CD4+/CD8-phenotype, whereas no

CD40L-expressing tumor cells could be found in B-cell NHL and HD. Among T-cell acute lymphoblastic leukemias, CD40L was detected only on 2 cases displaying a stem-cell-like phenotype. In follicular B-cell lymphomas a large number of CD40L-expressing CD3+/CD4+ T lymphocytes were found admixed with tumor cells within the neoplastic follicles and in their surrounding areas. In the nonfollicular B-cell lymphomas, CD40L-positive CD3+/CD4+ T lymphocytes were few or absent. In all HD subtypes other than the nodular lymphocytic predominance, CD40L-expressing CD3+/CD4+ T lymphocytes were numerous in the HD-involved areas and were mainly located in close proximity to the Reed-Sternberg cells. Our data indicate that in human lymphomas CD40L is preferentially expressed by a restricted subset of T-cell lymphomas, mostly with CD4 immunophenotype. Finally, we have provided morphological evidence that CD40L may play an important role in the cell contact-dependent interaction of tumor B-cells (CD40+) within the neoplastic follicles or Reed-Sternberg cells (CD40+) in HD-involved areas and the microenvironmental CD3+/CD4+/CD40L+ T lymphocytes.

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All 1644
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10180161 BIOSIS NO.: 199698635079

The expression of CD26 and CD40 ligand is mutually exclusive in human T-cell non-Hodgkin's lymphomas/leukemias.

AUTHOR: Carbone Antonino(a); Gloghini Annunziata; Zagonel Vittorina; Aldinucci Donatella; Gattei Valter; Degan Massimo; Improta Salvatore; Sorio Roberto; Monfardini Silvio; Pinto Antonio

AUTHOR ADDRESS: (a)Div. Pathol., Centro Regionale Riferimento Oncologico, IRCCS, via Pedemontana Occidentale, Aviano**Italy

JOURNAL: Blood 86 (12):p4617-4626 1995

ISSN: 0006-4971

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: CD26 and CD40 ligand (CD40L) are surface molecules on human activated T lymphocytes that play a critical role in the regulation of lymphopoiesis. Both molecules are expressed on a restricted fraction of human T-cell non-Hodgkin's lymphomas (NHL)/leukemias; however, little is known about their functional and/or clinical significance in these disorders. In this study, the pattern of expression of CD40L was compared with that of the CD26 molecule. A series of 67 human T-cell NHL/leukemias and a panel of leukemia/lymphoma T-cell lines were evaluated by immunohistochemistry, flow cytometry, and RNA studies. The overall frequency of CD26+ and CD40L+ samples was rather similar (25/67 (37%) v 18/67 (27%)). However, the majority of CD26-expressing cases clustered in the lymphoblastic lymphomas (LBL)/T-acute lymphoblastic leukemias (ALL; 12/23) and CD30+ anaplastic large-cell (ALC) lymphomas (5/8), whereas CD40L+ lymphomas included a large fraction of mycosis fungoides (11/21 (52%)). CD26 and CD40L coexpression was found only in 2 mycosis fungoides cases and 1 small lymphocytic lymphoma. Thus, the expression of the two antigens was mutually exclusive in almost all T-cell lymphomas/leukemias. Accordingly, lymphoma cell lines expressed either one of the molecules or the relative amounts of CD26 and CD40L were inversely proportional. In contrast, reactive T lymphocytes from patients with non-neoplastic T-cell expansions and in vitro activated CD3+ or CD4+ normal T cells were found to coexpress CD40L and CD26. Results of a multivariate analysis showed that the expression of CD26 in T-cell LBL/ALL patients was associated to a worse outcome in terms of survival, as compared with patients with CD26-tumors (P ltoreq .0001). Based on our results, it can be concluded that, (1) as opposed to activated or reactive normal T cells, the expression of CD26 and of CD40L is mutually exclusive in human T-cell lymphomas/leukemias; (2) expression of CD26 is restricted to aggressive pathologic entities, such as T-cell LBL/ALL and T-cell CD30+ ALC lymphomas, whereas CD40L is expressed on slow progressing diseases such as mycosis fungoides; and (3) within the T-cell LBL/ALL

group of tumors, CD26 may identify a subset of poor prognosis patients.

7/7/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11285304 BIOSIS NO.: 199800066636
CD40L is not expressed on T cells infiltrating non-Hodgkin's lymphoma B cells and is poorly induced after stimulation.
AUTHOR: Finke J; Molto L; Bloom T; Kolenko V; Pohlman B; Lichtin A; McLain D; Tubbs R; Bukowski R M
AUTHOR ADDRESS: Cleveland Clinic Foundation, Cleveland, OH**USA
JOURNAL: Blood 90 (10 SUPPL. 1 PART 1):p76A Nov. 15, 1997
CONFERENCE/MEETING: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

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11624464 BIOSIS NO.: 199800406742
Localization in situ of costimulatory molecules and cytokines in B-cell non-Hodgkin's lymphoma.
AUTHOR: Vyth-Dreese F A(a); Boot H; Dellemijn T A M; Majoor D M; Oomen L C J M; Laman J D; Van Meurs M; De Weger R A; De Jong D
AUTHOR ADDRESS: (a)Div. Immunol., Netherlands Cancer Inst., Plesmanlaan 121, 1066 CX Amsterdam**Netherlands
JOURNAL: Immunology 94 (4):p580-586 Aug., 1998
ISSN: 0019-2805
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Costimulatory molecules are essential in cognate interactions between T and B lymphocytes. To study the prerequisites of functional interactions between malignant B cells and intermingled T cells in B-cell non-Hodgkin's lymphomas (B-NHL), we examined the expression of CD40, CD80 and CD86 and their ligands CD40 ligand (CD40L, CD154), CD28 and CTLA4 (CD152) using immunohistochemistry and confocal laser scanning microscopy. Almost all mucosa-associated lymphoid tissue (MALT) NHL were positive for CD40 and CD80 and in nine out of 14 cases were positive for CD86. The majority of follicle centre cell lymphomas (FCCL) expressed CD40, but were heterogeneous in their expression of CD80 and CD86. Most diffuse large cell lymphomas (DLCL) were CD80+, but lacked expression of CD86. These patterns reflect the differences in phenotype of normal marginal-zone B cells (as counterparts of MALT NHL) and germinal centre cells (as counterparts of FCCL and DLCL). Counter-receptors on T cells were detectable in 13 of 14 MALT NHL, 12 of 16 FCCL but only occasionally in DLCL (three of 12 cases). A subgroup of FCCL was identified with T-cell expression of CD40L, CD28 and CTLA4 simultaneously with strong expression of CD40 and CD86 on the tumour B cells. These results indicate that MALT NHL and a subset of FCCL are most optimally equipped for functional interactions with T cells. This may be supported by the demonstration of cytokine production mainly in T cells - in MALT NHL (interleukin-2 (IL-2), interferon-gamma (IFN-gamma), IL-10) and FCCL (IL-2, IFN-gamma) and to a lesser extent in DLCL.

BIOSIS NO.: 200100338274
Phase I study of recombinant human CD40 ligand in cancer patients.

LANGUAGE: English

ABSTRACT: The precise mechanisms regulating T-helper function have been intensively investigated. We and others have recently identified a novel T-cell- B-cell-activating molecule called T-BAM that directs B-cell differentiation by interacting with the CD40 molecule on B cells. Using a specific monoclonal antibody against T-BAM (5C8), we have previously shown that T-BAM expressing T cells are predominantly CD4+CD8- and in normal lymphoid tissue have a unique distribution. However, no information has been obtained regarding the phenotype and functional properties of human neoplastic T cells. Therefore, we investigated T-BAM expression immunohistochemically in 87 well-characterized T-cell non-Hodgkin's lymphomas and lymphoid leukemias (LL). We found that 21/84 neoplasms expressed detectable T-BAM and these positive tumors belong almost exclusively to the CD4+CD8- subtype. In addition, to determine whether T-BAM expression could be induced on T-BAM-LL cells, we activated T-BAM-LLs in vitro and showed that T-BAM could be upregulated only in CD4+CD8- tumors. Our studies clearly show that T-BAM is constitutively expressed in a large number of T-cell neoplasms with a relative mature phenotype (CD4+CD8-) and that only CD4+ neoplastic T cells can be induced in vitro to express this molecule. Additional studies are necessary to identify the biologic significance of T-BAM expression and its potential and clinical implications.

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09687091 BIOSIS NO.: 199598142009

Expression of functional CD40 antigen on Reed-Sternberg cells and Hodgkin's disease cell lines.

AUTHOR: Carbone Antonino(a); Gloghini Annunziata; Gattei Valter; Aldinucci Donatella; Degan Massimo; De Paoli Paolo; Zagonel Vittorina; Pinto Antonio

AUTHOR ADDRESS: (a)Div. Pathol., Centro Regionale di Riferimento Oncologico, IRCCS, via Pedemontana Occidentale, Av**Italy

JOURNAL: Blood 85 (3):p780-789 1995

ISSN: 0006-4971

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: CD40 is a member of the nerve growth factor receptor family, showing a significant homology to the Hodgkin's disease (HD)-associated antigen CD30 and is capable of transduce growth signals in a number of cell types. A series of 312 lymphoma samples, including 139 cases of HD, 32 cases of CD30+ anaplastic large cell (ALC) lymphomas, 141 cases of other non-Hodgkin's lymphomas (NHLs), and a panel of HD- or NHL-derived cell lines, were evaluated for CD40 expression by immunostaining of paraffin embedded sections, cell smears and flow cytometry. CD40 was strongly expressed with a highly distinct pattern of staining on Reed-Sternberg (RS) cells and variants in 100% (139/139) of HD cases, irrespective of their antigenic phenotype (T, B, non T-non B) and histologic subtype of HD. Conversely, CD40 was immunodetected on only one third (12/32; 37%) of ALC lymphoma cases and on 105 of 127 B-cell NHLs. The relative cell density of CD40 on HD cell lines (L-428, KM-H2, HDLM-2) as assessed by flow cytometry was significantly higher than on all other lymphoma cells analyzed. Engagement of CD40 by its soluble ligand (CD40L) enhanced both clonogenic capacity and colony cell survival of HD cell lines. Such effect was potentiated by interleukin-9 costimulation in KM-H2 cells. Finally, we have shown that in vitro rosetting of activated CD4+ T cells to HD cells (L-428) is mediated in part by the CD40/ CD40L adhesion pathway. Our data indicate that CD40 is a useful antigen for immunodetection and identification of tumor cells in all subtypes of HD, and suggest that it may play a role in the regulation of RS cell expansion and the contact-dependent interactions of these cells with cytokineproducing T lymphocytes.

FF/31 (Item 31 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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09860255 BIOSIS NO.: 199598315173

Functional Expression of Adhesion Receptors and Costimulatory Molecules by
Fresh and Immortalized B-Cell Non-Hodgkin's Lymphoma Cells.

AUTHOR: Vyth-Dreese Florry A(a); Dellempijn Trees A M; Van Oostveen Johan W;
Feltkamp Constance A; Hekman Annemarie

AUTHOR ADDRESS: (a)Div. Immunol., Netherlands Cancer Inst., Plesmanlaan
121, 1066 CX Amsterdam**Netherlands

JOURNAL: Blood 85 (10):p2802-2812 1995

ISSN: 0006-4971

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Peripheral blood lymphocytes of a patient with follicular B-cell non-Hodgkin's lymphoma (B-NHL) were immortalized in vitro by Epstein-Barr virus (EBV). Eight cell lines were obtained (termed BNS1, BNS2-1 through BNS2-7), which showed a pattern of idiotypic (id) Ig surface expression and Ig JH and kappa gene rearrangement, identical to that of the parent cells (termed NS), confirming their neoplastic origin. Induction of allogeneic T-cell proliferation by NS cells was mediated by HLA-DR, leukocyte function-associated antigen-1 (LFA-1), LFA-3, B7-1/CD80, and CTLA4 and resulted in the upregulation (LFA-3, intercellular adhesion molecule-1 (ICAM-1), CD40) and induction (B7-1/CD80, B7-2/CD86, L16/activated LFA-1) of accessory molecules on NS cells. In turn, responder T lymphocytes were induced to express B7-1/CD80, B7-2/CD86, CD40 ligand (CD40L), ICAM-1, L16/activated LFA-1, and HLA-DR, reflecting bidirectional signaling between T lymphocytes and B-NHL cells. Preactivation of NS cells by EBV transformation or CD40 engagement resulted in enhanced expression of accessory molecules and abolished the requirement for accessory cells during allostimulation. These resting and activated clonal B cells will be useful in further dissecting the requirements for B-NHL costimulation.

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10064605 BIOSIS NO.: 199598519523

CD40 ligand is constitutively expressed in a subset of T cell
lymphomas and on the microenvironmental reactive T cells of follicular
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AUTHOR: Carbone Antonino(a); Gloghini Annunziata; Gruss Hans-Jurgen; Pinto
Antonio

AUTHOR ADDRESS: (a)Div. Pathol., Centro Regionale Riferimento Oncol.,
IRCCS, via Pedemontana Occidentale, Aviano I-**Italy

JOURNAL: American Journal of Pathology 147 (4):p912-922 1995

ISSN: 0002-9440

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Although CD40 has been extensively studied in B and T-cell non-Hodgkin's lymphomas (NHLs)/leukemias, and more recently in Hodgkin's disease (HD), little is known about the expression of its ligand (CD40L) in lymphoproliferative disorders other than T-cell NHLs/leukemias. A series of 121 lymphoma/leukemia samples, including 35 cases of HD, 34 T-cell and 39 B-cell NHLs, 2 cases of adult T-cell leukemia/lymphoma, and 11 cases of T-cell acute lymphoblastic leukemia, were evaluated for CD40L expression by immunostaining of frozen tissue sections and flow cytometry with the anti-CD40L monoclonal antibody M90. CD40L was constitutively expressed by neoplastic cells in 15 of 36 (42%) T-cell NHLs/adult T-cell leukemia/lymphomas, almost invariably those displaying the CD4+/CD8-phenotype, whereas no

group of tumors, CD26 may identify a subset of poor prognosis patients.

7/7/21 (Item 21 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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11285304 BIOSIS NO.: 199800066636
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AUTHOR: Finke J; Molto L; Bloom T; Kolenko V; Pohlman B; Lichtin A; McLain D; Tubbs R; Bukowski R M
AUTHOR ADDRESS: Cleveland Clinic Foundation, Cleveland, OH**USA
JOURNAL: Blood 90 (10 SUPPL. 1 PART 1):p76A Nov. 15, 1997
CONFERENCE/MEETING: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

11624464 BIOSIS NO.: 199800406742
Localization in situ of costimulatory molecules and cytokines in B-cell non-Hodgkin's lymphoma.
AUTHOR: Vyth-Dreese F A(a); Boot H; Dellemijn T A M; Majoor D M; Oomen L C J M; Laman J D; Van Meurs M; De Weger R A; De Jong D
AUTHOR ADDRESS: (a)Div. Immunol., Netherlands Cancer Inst., Plesmanlaan 121, 1066 CX Amsterdam**Netherlands
JOURNAL: Immunology 94 (4):p580-586 Aug., 1998
ISSN: 0019-2805
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Costimulatory molecules are essential in cognate interactions between T and B lymphocytes. To study the prerequisites of functional interactions between malignant B cells and intermingled T cells in B-cell non-Hodgkin's lymphomas (B-NHL), we examined the expression of CD40, CD80 and CD86 and their ligands CD40 ligand (CD40L, CD154), CD28 and CTLA4 (CD152) using immunohistochemistry and confocal laser scanning microscopy. Almost all mucosa-associated lymphoid tissue (MALT) NHL were positive for CD40 and CD80 and in nine out of 14 cases were positive for CD86. The majority of follicle centre cell lymphomas (FCCL) expressed CD40, but were heterogeneous in their expression of CD80 and CD86. Most diffuse large cell lymphomas (DLCL) were CD80+, but lacked expression of CD86. These patterns reflect the differences in phenotype of normal marginal-zone B cells (as counterparts of MALT NHL) and germinal centre cells (as counterparts of FCCL and DLCL). Counter-receptors on T cells were detectable in 13 of 14 MALT NHL, 12 of 16 FCCL but only occasionally in DLCL (three of 12 cases). A subgroup of FCCL was identified with T-cell expression of CD40L, CD28 and CTLA4 simultaneously with strong expression of CD40 and CD86 on the tumour B cells. These results indicate that MALT NHL and a subset of FCCL are most optimally equipped for functional interactions with T cells. This may be supported by the demonstration of cytokine production mainly in T cells - in MALT NHL (interleukin-2 (IL-2), interferon-gamma (IFN-gamma), IL-10) and FCCL (IL-2, IFN-gamma) and to a lesser extent in DLCL.

BIOSIS NO.: 200100338274
Phase I study of recombinant human CD40 ligand in cancer patients.

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BB145. A2 B56

AUTHOR: Vonderheide Robert H(a); Dutcher Janice P; Anderson Jeanne E;
Eckhardt S Gail; Stephans Katherine F; Razvillas Betty; Garl Susan;
Butine Michael D; Perry Vicki P; Armitage Richard J; Ghalie Richard;
Caron Dania A; Gribben John G
AUTHOR ADDRESS: (a)Dana-Farber Cancer Institute, 44 Binney St, Boston, MA,
02115; robertvonderheide@dfci.harvard.edu**USA
JOURNAL: Journal of Clinical Oncology 19 (13):p3280-3287 July 1, 2001
MEDIUM: print
ISSN: 0732-183X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

B 0254. J75

ABSTRACT: Purpose: To determine the toxicity, maximum-tolerated dose (MTD), and pharmacokinetics of recombinant human CD40 ligand (rhuCD40L) (Avrend; Immunex Corp, Seattle, WA), suggested in preclinical studies to mediate cytotoxicity against CD40-expressing tumors and immune stimulation. Patients and Methods: Patients with advanced solid tumors or intermediate- or high-grade non-Hodgkin's lymphoma (NHL) received rhuCD40L subcutaneously daily for 5 days in a phase I dose-escalation study. Subsequent courses were given until disease progression. Results: Thirty-two patients received rhuCD40L at three dose levels. A total of 65 courses were administered. The MTD was 0.1 mg/kg/d based on dose-related but transient elevations of serum liver transaminases. Grade 3 or 4 transaminase elevations occurred in 14%, 28%, and 57% of patients treated at 0.05, 0.10, and 0.15 mg/kg/d, respectively. Other toxicities were mild to moderate. At the MTD, the half-life of rhuCD40L was calculated at 24.8+-22.8 hours. Two patients (6%) had a partial response on study (one patient with laryngeal carcinoma and one with NHL). For the patient with laryngeal cancer, a partial response was sustained for 12 months before the patient was taken off therapy and observed on no additional therapy. Three months later, the patient was found to have a complete response and remains biopsy-proven free of disease at 24 months. Twelve patients (38%) had stable disease after one course, which was sustained in four patients through four courses. Conclusion: The MTD of rhuCD40L when administered subcutaneously daily for 5 days was defined by transient serum elevations in hepatic transaminases. Encouraging antitumor activity, including a long-term complete remission, was observed. Phase II studies are warranted.

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<u>L4</u>	(gp39 or 5c8 or cd40 adj ligand) and (non adj Hodgkin\$)	42	<u>L4</u>
<u>L3</u>	(cd40L) and (non adj Hodgkin\$)	62	<u>L3</u>
<u>L2</u>	(cd40L) same (non adj Hodgkin\$)	7	<u>L2</u>
<u>L1</u>	(cd20 or cd40L) same (non adj Hodgkin\$)	48	<u>L1</u>

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GP39S	0
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5C8S	0
CD40.DWPI,EPAB,JPAB,USPT,PGPB.	1118
CD40S	0
LIGAND.DWPI,EPAB,JPAB,USPT,PGPB.	64061
LIGANDS.DWPI,EPAB,JPAB,USPT,PGPB.	43602
NON.DWPI,EPAB,JPAB,USPT,PGPB.	2313297
NONS.DWPI,EPAB,JPAB,USPT,PGPB.	28
HODGKIN\$	0
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*DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ*L4 (gp39 or 5c8 or cd40 adj ligand) and (non adj Hodgkin\$)42 L4L3 (cd40L) and (non adj Hodgkin\$)62 L3L2 (cd40L) same (non adj Hodgkin\$)7 L2L1 (cd20 or cd40L) same (non adj Hodgkin\$)48 L1

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Term	Documents
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GP39S	0
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5C8S	0
CD40.DWPI,EPAB,JPAB,USPT,PGPB.	1118
CD40S	0
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LIGANDS.DWPI,EPAB,JPAB,USPT,PGPB.	43602
NON.DWPI,EPAB,JPAB,USPT,PGPB.	2313297
NONS.DWPI,EPAB,JPAB,USPT,PGPB.	28
HODGKINS\$	0
((GP39 OR 5C8 OR CD40 ADJ LIGAND) AND (NON ADJ HODGKINS\$)).USPT,PGPB,JPAB,EPAB,DWPI.	42

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L1: Entry 20 of 48

File: USPT

Jun 4, 2002

DOCUMENT-IDENTIFIER: US 6399068 B1

TITLE: Method of treatment with a non-antigenic toxin-conjugate and fusion protein of internalizing receptor system

Brief Summary Paragraph Right (5):

The CD20 antigen, in contrast to the CD22 antigen, is a quite highly expressed B-cell restricted antigen that is expressed on a wide range of B-cell malignancies, ranging from acute lymphocytic leukemia (ALL) to the more differentiated B-Cell (B-CLL) and non-Hodgkin's lymphoma (NHL), and even to hairy cell leukemia (HCL). It generally is expressed on cells in the vast majority of cases of these malignancies at a high antigen density. A major disadvantage of CD20 is that it is a slowly internalizing antigen. For RAIT directed against CD20 this feature may not be a problem, but it militates significantly against the use of CD20 for toxin-based therapy.

CLAIMS:

4. A method as claimed in claim 1, wherein said cell marker is CD20 and said subject has B-cell lymphocytic leukemia, non-Hodgkin's lymphoma, hairy cell leukemia or acute myelogenous leukemia.

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L1: Entry 21 of 48

File: USPT

Jun 4, 2002

DOCUMENT-IDENTIFIER: US 6399061 B1

TITLE: Chimeric and radiolabelled antibodies specific to human CD20 antigen and use thereof for treatment of B-cell lymphoma

Brief Summary Paragraph Right (17):

Therefore, an approach at improving the ability of murine monoclonal antibodies to be effective in the treatment of B-cell disorders has been to conjugate a radioactive label or toxin to the antibody such that the label or toxin is localized at the tumor site. For example, the above-referenced IF5 antibody has been "labeled" with iodine-131 (.sup.131 I) and was reportedly evaluated for biodistribution in two patients. See Eary, J. F. et al., "Imaging and Treatment of B-Cell Lymphoma" J. Nuc. Med. 31/8:1257-1268 (1990); see also, Press, O. W. et al., "Treatment of Refractory Non-Hodgkin's Lymphoma with Radiolabeled MB-1 (Anti-CD37) Antibody" J. Clin. Onc. 7/8:1027-1038 (1989) (indication that one patient treated with .sup.131 I-labeled IF-5 achieved a "partial response"); Goldenberg, D. M. et al., "Targeting, Dosimetry and Radioimmunotherapy of B-Cell Lymphomas with Iodine-131-Labeled LL2 Monoclonal Antibody" J. Clin. Onc. 9/4:548-564 (1991) (three of eight patients receiving multiple injections reported to have developed a HAMA response); Appelbaum, F. R. "Radiolabeled Monoclonal Antibodies in the Treatment of Non-Hodgkin's Lymphoma" Hem./Onc. Clinics of N.A. 5/5:1013-1025 (1991) (review article); Press, O. W. et al "Radiolabeled-Antibody Therapy of B-Cell Lymphoma with Autologous Bone Marrow Support." New England Journal of Medicine 329/17: 1219-12223 (1993) (iodine-131 labeled anti-CD20 antibody IF5 and B1); and Kaminski, M. G. et al "Radioimmunotherapy of B-Cell Lymphoma with [.sup.131 I] Anti-B1(Anti-CD20) Antibody". NEJM 329/7 (1993) (iodine-131 labeled anti-CD20 antibody B1; hereinafter "Kaminski").